9. SITE MONITORING BY WESTAT/DCP MONITORING CONTRACTOR

NIH guidelines specify that all clinical trials have a system in place for appropriate oversight and monitoring to ensure the safety of participants and the validity of the data. Westat CRAs conduct a site initiation visit, annual/interim visits at the lead organization until participant followup is complete, and a closeout visit at the lead organization. The lead organization is responsible for the oversight and monitoring of the participating organizations.

9.1 Three Types of Site Visits

Westat CRAs conduct three types of site visits at the lead organization: initiation, annual/interim, and closeout visits. Each of these is discussed separately below. DCP representatives may choose to participate in each of these visits.

9.1.1 Initiation Visit

Purpose

The purposes of the initiation visit are to:

- Meet with key staff (PI, Site Coordinator, pharmacist, lab technician, etc.) at the lead organization. If participating organizations are involved, it is expected that key staff from each of them are present at the lead organization for the visit.
- Review and discuss aspects of the protocol and study procedures as outlined.
- Answer questions by research study staff as they relate to trial operations.
- Identify key site staff and discuss specific study responsibilities.
- Discuss and identify outstanding issues that require resolution before study participants are enrolled.
- Tour facilities to determine that they are adequate for study purposes.

- Orient staff to all general aspects of the performance of the work to assure a successful trial.
- Discuss the roles and responsibilities of DCP, clinical site staff, and Westat staff.

Scheduling

The initiation visit is usually accomplished in 1 day and occurs when the site is ready to begin the study. Criteria for site initiation visit readiness include DCP PIO and local IRB approval of the protocol, IND readiness (as appropriate), availability of the investigational agent at the site, and the availability of qualified site staff. Westat coordinates timing of the visit with DCP and the PI or Site Coordinator. Westat sends a confirmation email and an agenda in advance of the initiation visit. DCP approves the agenda.

Conduct of Visit

Topics discussed at an initiation visit include, but are not limited to, the following:

- Role of DCP staff;
- Role of the lead organization;
- Role of the participating organizations (if applicable);
- Background and purpose of study;
- Study procedures;
- Participant enrollment;
- Participant recruitment and retention strategies;
- Adverse Event and Serious Adverse Event reporting;
- Toxicity management;
- Study agent discontinuation;
- Data collection and data management;
- Source documentation/confidentiality;

- Policy and procedures manuals and other resources;
- Regulatory documentation and role of the regulatory contractor;
- Recordkeeping requirements;
- Laboratory procedures;
- Monitoring frequency;
- Unblinding procedures;
- Pharmacy;
- Quality Assurance (QA) procedures;
- Communication;
- Handling protocol deviations;
- Site monitoring of lead organization; and
- Site monitoring of any participating organization(s).

An initiation visit typically includes a tour of the physical facility, which includes the laboratories, pharmacy, and clinical examination rooms. A tour may also include the office of the Site Coordinator or research nurse to show where the research records will be kept.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will complete the Initiation Visit Report, which is reviewed by DCP. A copy of the report format is in Appendix F.

Site personnel will receive a copy of this DCP approved site visit report 4-6 weeks after the visit. The PI and/or Site Coordinator must submit a followup letter to DCP outlining the institution's plan to resolve any action items including the action to be taken, the person responsible for the action, and the timeframe for completion. The followup letter must be sent to the DCP Medical Monitor and/or Nurse Specialist within 30 days of receipt of the site visit report.

9.1.2 Annual/Interim Visit

Purpose

Monitoring visits are conducted annually at the lead organization until participant followup is complete. In addition, an interim visit at the lead organization can be scheduled at any time if the protocol is rapidly accruing or if deficiencies are discovered. The purpose of the annual/interim site visit is to determine that:

- There is compliance with the study protocol or investigational plan;
- Changes to the protocol and/or consent document have been approved by the IRB and NCI;
- Changes to the consent document have been explained to participants and a revised consent document has been signed by participants who are still on study;
- Source documentation is adequate and CRFs are completed appropriately;
- CRF data have been entered into the database of record;
- Protocol deviations are recorded and reported according to DCP procedures;
- Participants have signed an informed consent document prior to the conduct of study visits and/or study procedures;
- There is accurate reporting of significant events such as AEs and SAEs;
- Accurate, complete, and timely reports are being made to DCP and the IRB; and
- The investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.

Scheduling

Each annual/interim monitoring visit is accomplished in 2 or 3 days at the lead organization. Westat will discuss plans to conduct the visit with DCP and the PI or Site Coordinator at least 6 weeks in advance of the visit. Westat will send a letter confirming the visit to the PI and Site Coordinator stating the purpose and objectives of the visit, the staff and documents to be made available, and the expected duration of the visit. At least 2 weeks prior to the visit, the CRA will notify the Site Coordinator of charts

to be reviewed. At least two additional charts (not previously requested) from the lead organization will be reviewed at each annual/interim visit.

Requirements

The following must be available for the CRA upon arrival for a site visit:

- Site monitoring visit log;
- Participant identification logbook (if applicable);
- CRFs notebooks or folders;
- Binders containing copies of signed informed consents for all study participants;
- Source documentation, including clinic charts, shadow files, and hospital charts if relevant;
- Regulatory documents;
- Appointment to meet with the site pharmacist, when a pharmacy audit is being performed; and
- A quiet well-lit area for the CRA's use each day during the site visit.

In addition, the Site Coordinator or designated staff should be available each day to review findings and provide additional records that may be requested by the CRA. Time should be set aside at the conclusion of the visit for the Site Coordinator and PI to meet with the CRA to discuss the findings, site performance parameters, and any outstanding issues.

Conduct of Visit

The CRA will perform the following tasks during the annual/interim visit at the lead organization:

- Confirm that the following regulatory documents are on file:
  - NCI/IRB approval letters;
  - NCI/IRB letters of annual approval;

- NCI/IRB-approved consents;
- Form FDA 1572s and appropriate professional licensure;
- Laboratory certificates;
- Laboratory normal values;
- Screening logs;
- Safety reports and memos with appropriate IRB correspondence;
- Other IRB correspondence; and
- Human subjects protection training.

■ Ensure that sensitive documents are stored appropriately.

■ Perform CRF and record review. The following data will be verified against source documents:

- Signed and dated informed consent document, obtained prior to the pre-entry workup;
- Inclusion/exclusion criteria;
- Visit dates;
- Clinical and laboratory evaluations;
- Concomitant medications;
- Adverse Events and Serious Adverse Events;
- Concurrent illness; and
- Adherence to protocol.

The number of records that will be reviewed is dependent upon the number of participants enrolled in the study. Records will be selected from the lead organization.

The CRA will verify eligibility and perform chart reviews for a minimum of seven charts or 25 percent (whichever is greater) of participant records per study at the lead organization. Informed

consent documents will be reviewed for 100 percent of enrolled participants at the lead organization. The Westat CRA will also:

- Review a sample of completed CRFs against entries in the database of record;
- Conduct pharmacy audit:
  - Review of pharmacy-related regulatory documentation;
  - Examine procedures for:
    1. Investigational agent storage;
    2. Investigational agent distribution; and
    3. Investigational agent security.
  - Compare shelf inventory (bottle count) against the balance as stated on the NCI Drug Accountability Record Form (DARF);
  - Audit participant records to compare investigational agent dispensed as recorded on the DARF versus that recorded as administered in the source document;
  - Compare the DARF with the protocol registration listing to ensure that participants who received investigational agents were registered on the specified protocol; and
  - Authenticate that any unopened/unused or expired investigational agent containers are returned to DCP.
- Assess site operations:
  - Verify adequate resources (e.g., facilities, staffing database);
  - Review internal QA activities;
  - Review accrual of participants available/recruited for the study;
  - Inquire about and note if database used for study-specific procedures;
  - Follow up on problems previously identified;

The CRA will conduct a summary meeting with the PI and study staff to review the findings of the site visit. The DCP Medical Monitor, Project Officer, and/or nurse specialist often attend this summary meeting, either in person or via teleconference.

- During this meeting the findings identified during the course of the site monitoring visit will be discussed, and recommendations for improvement will be made; and
- Review the oversight of participating organizations by the lead organization.

Followup

At the conclusion of the visit, issues that require followup will be discussed. Within 24 hours of completion of the visit, the CRA will send a preliminary report to DCP that lists an overall rating for items reviewed, based on the presence or absence of deficiencies found. A copy of the report format is in Appendix G. The CRA will then complete the full Annual Visit Report and Pharmacy Audit Report, which are reviewed by DCP. A copy of the Annual Visit Report format may be found in Appendix G; a copy of the Pharmacy Audit Report is in Appendix I. Site personnel will receive a copy of the reports 4-6 weeks after the visit, once they have been finalized and approved by DCP.

9.1.3 Close-out Visit

Purpose

A Westat CRA will typically conduct a closeout visit at the lead organization after the "draft final report" has been submitted to DCP, but before the final version of the report is submitted. The duration of the visit is usually 1-2 days. The purpose of this visit is to:

- Formally bring closure to the study at the site;
- Ensure that all data have been collected;
- Complete the final accounting and disposition of the study agent; and
- Verify that the investigator's files are complete.

The closeout visit for a particular protocol may be combined with elements of an annual site visit in specific situations. In these situations, the combined annual/closeout visit usually lasts 2-3 days.

Scheduling

A closeout visit will generally take 1 day, but may require more. Westat will discuss plans to conduct the visit with DCP and the PI or Site Coordinator at least 6 weeks in advance of the visit. Westat will send a letter confirming the visit to the PI and Site Coordinator stating the purpose and objectives of the visit, the staff and documents to be available at the lead organization, and the expected duration of the visit.

Requirements

The requirements for a closeout visit are the same as for an annual/interim visit (see Section 9.1.2).

Conduct of Visit

During the visit, the Westat CRA will perform the following:

- Ensure that all CRFs for each participant have been completed:
  - Verify that all data have been keyed onsite or all forms have been submitted to the lead organization or the protocol-specified destination;
  - If the data forms have not been completed, keyed, or submitted, the CRA will discuss with the investigator and Site Coordinator a timeline for accomplishing these tasks.
- Verify that a signed informed consent document is on file for each study participant.
- Review the status of all outstanding data edits, queries, or delinquent forms and timeline for their resolution.
- Confirm that the IRB/IEC has been informed of the study closure.

- Verify that all regulatory and other pertinent documents for the protocol (IRB approvals, consent documents, etc.) are current and on file.

- Verify that the investigator knows to submit a final report to DCP and that a deadline for completion has been identified.

- Ensure that a progress note is included in each participant's medical record indicating that study participation has ended.

- Ensure that the PI understands the requirements for including Adverse Events in the final report for participants who have completed the study.

- Ensure that the PI understands the requirements for retention of study records. (The investigator may refer to the award document which specifies the time for record retention).

- If applicable, determine the disposition of participant specimens obtained during the study and stored on site. Ensure that all specimens have been sent to the appropriate place/facility or that the PI understands the plan for future shipment.

- Meet with the site pharmacist to determine the disposition of remaining study agent and ensure that it has been returned to the repository. Ensure that all required study agent accountability has been reconciled and forms have been completed appropriately. If a blinded study agent was used, confirm that the tear-off labels were not opened. For any that were opened, documentation should be obtained noting the reason for unblinding.

Followup

At the conclusion of the visit, issues that require followup will be discussed. The CRA will complete the Close-Out Visit Report, which is reviewed by DCP. A copy of the report format is in Appendix H. Site personnel will receive a copy of this report 4-6 weeks after the visit, once the report has been finalized and approved by DCP.